



A comparison of the onset of action of salbutamol and formoterol in reversing methacholine-induced bronchoconstriction

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This single-centre, randomized, double-blind, double-dummy four-way cross-over study in 24 moderately severe asthmatic patients compared the speed of onset of recommended doses of salbutamol (200 μ g) and formoterol (12 μ g) delivered by metered-dose inhaler in reversing the bronchoconstriction induced by a cumulative dose of methacholine to produce a 20% decrease (PD₂₀) in forced expiratory volume in 1 s (FEV₁).

Specific airway conductance (SGAW) and airway resistance (RAW) were measured in baseline condition, immediately after challenge and 0.5, 1.5, 3, 5, 10, 15, 30, 60 min and every hour up to 4 h after inhalation of the trial drug. FEV₁ was measured in baseline condition, after challenge and 15, 30 and 60 min and then every 30 min up to 4 h after inhalation of the study drug. The primary efficacy parameter was the change in SGAW.

Salbutamol produced a two-fold increase in SGAW within 4 min and a maximum increase after 79.3 min. Formoterol produced a two-fold increase in SGAW after 5 min and a maximum increase after 119.6 min. Changes in SGAW were slightly, but consistently, higher during the first 2 h after inhalation of salbutamol, both in absolute values and as a percentage of the maximum response. Differences were significant at 10, 15 and 30 min time points. There was no significant difference between the maximum values of SGAW after the two drugs. Changes in RAW and FEV₁ reflected the differences in SGAW.

It was concluded that in methacholine-induced bronchoconstriction both formoterol and salbutamol have a very fast onset of action, achieving prechallenge values of SGAW within 3 min, salbutamol being slightly faster than formoterol.

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Introduction

Short-acting inhaled β_2 -agonists such as salbutamol are widely used for the treatment of acute asthma attacks. Salbutamol acts quickly to relieve bronchoconstriction but its duration of action is relatively short (4–6 h) (1). The number of puffs of salbutamol used by a patient gives a good indication of the degree of actual asthma control.

Long-acting β_2 -agonists such as salmeterol and formoterol have a bronchodilatory effect that lasts for up to 12 h (2–6). They are recommended as asthma maintenance therapy in international guidelines and have been reserved by regulatory authorities for this purpose.

An important characteristic of an acute treatment is the speed of onset and the time to relief of symptoms. *In vitro* studies using isolated guinea-pig trachea have generated conflicting results: a study of the effect of drugs on isolated preparations contracted with carbachol found the onsets of

action of formoterol and salbutamol to be similar (7). However, a study on electrically stimulated preparations found that for salbutamol the time to attain 50% of the half maximal response was about 3 min whereas for formoterol the time was 8 min (8). A number of clinical studies in situations of spontaneous bronchoconstriction have demonstrated that both drugs have rapid onsets of action (3,4,6).

A shortcoming of these studies however, is the inter-individual variability in the degree of bronchoconstriction, with the consequence that it is difficult to study effects of different treatments in a controlled manner. It is preferable to standardize the level of bronchoconstriction, and this has been done using methacholine challenge (9), which closely mimics an attack of asthma. A number of studies have assessed the speeds of onset of action of bronchodilator drugs using this methodology but only one study (10) directly compared salbutamol and formoterol. This placebo-controlled study, which compared two doses of formoterol with salbutamol, concluded that both drugs had a rapid onset of action, with benefits apparent within 2 min. Assessment of airway function however, was based on measurement of FEV₁, which, being effort dependent, is a less sensitive procedure than the measurement of specific airway

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conductance (*SGAW*) (11,12), as was used in the present study. The rationale for the present study therefore was to compare the speeds of onset of recommended doses of salbutamol (200 µg) and formoterol (12 µg) following methacholine challenge, using the most sensitive methodology available for assessment of changes in airway calibre.

Methods

PATIENTS

Male and non-pregnant female patients with moderately severe asthma aged between 18 and 60 years, who were able to use a metered-dose inhaler correctly, had measurable airway responsiveness [cumulative dose of methacholine less than 1600 µg needed to produce a 20% decrease (PD_{20}) in FEV_1], had a baseline FEV_1 of less than 80% of the predicted value and demonstrated a reversibility in FEV_1 more than 15% of the baseline value following inhalation of 200 µg of salbutamol were included in the study. Patients were excluded if they had changed their regular asthma therapy, suffered from a respiratory tract infection or had an exacerbation of their asthma during the 4 weeks prior to the study. Patients were also excluded if they were being treated with any β -receptor antagonist or if they had taken any other experimental drug in the 30 days prior to the study.

The patients abstained from long-acting inhaled β_2 -agonists, oral β_2 -agonists, theophyllines or antihistamines at least 24 h prior to the methacholine challenge tests and had to abstain from short-acting inhaled β_2 -agonists for 12 h. Ipratropium bromide, other anticholinergic drugs or astemizole were not permitted at any time during the study. The following drugs were permitted if taken in a stable dose: nedocromil sodium, cromolyn sodium, antihistamines and oral and/or inhaled corticosteroids up to a maximum of 800 µg day⁻¹ (400 µg day⁻¹ of fluticasone propionate). The study was approved by the local medical ethics committee and informed consent was obtained from all patients. The study was conducted according to the Declaration of Helsinki as modified by the Hong Kong Amendment 1989.

STUDY DESIGN

This was a single-centre, randomized, double-blind, double-dummy, four-period, four-treatment cross-over study. There being no data available on the variability of response of *RAW*, *SGAW* and FEV_1 following treatment with salbutamol or formoterol after methacholine challenge, the sample size was fixed for practical considerations as 24 evaluable patients. Each eligible patient was to receive a single dose of each of four treatments via a metered-dose inhaler on 4 different study days in random sequence ordered according to a randomly allocated row of a 4 × 4 William's Latin Square. The four treatments consisted of two pairs as detailed below:

Treatment 1A: salbutamol 200 µg followed immediately by formoterol placebo.

Treatment 1B: formoterol placebo followed immediately by salbutamol 200 µg.

Treatment 2A: formoterol 12 µg followed immediately by salbutamol placebo.

Treatment 2B: salbutamol placebo followed by formoterol 12 µg.

Thus the treatments within each pair were the same but the orders were reversed. This allowed for the possibility that the speeds of onset of action might be very rapid so that order of delivery of active treatment (before or after placebo) might have an important impact on the measured speed of response.

Patients made four study visits (visits 2–5) to the clinic, each being within 2–10 days of the preceding visit. The first of these visits was 1–7 days following an initial visit (visit 1) at which patient eligibility was determined. During visits 2–5 *RAW*, *SGAW* and FEV_1 were measured in baseline condition. Methacholine was administered by dosimeter according to a validated method (13) in doubling cumulative doses at 5-min intervals until FEV_1 had fallen by 20% or more. The challenge was then stopped and the patient monitored until FEV_1 had stabilized for at least 3 min. Postchallenge values of *RAW*, *SGAW* and FEV_1 were recorded and patients received one of four treatments according to the randomization sequence via a Volumatic® attached to a metered-dose inhaler.

RAW and *SGAW* were measured again in the same way 0.5, 1.5, 3, 5, 10, 15, 30, 60 min and every hour up to 4 h after inhalation of the study drugs. *RAW* and *SGAW* were measured in a pressure-compensated integrated flow plethysmograph (2800 Autobox; Sensormedics) as the chord slopes between inspiratory and expiratory flow of 0.5 l s⁻¹ at a respiratory rate of 0.5 Hz. Means of nine measurements were reported. Because of the limitation in time during the first 5 min three measurements were performed at each timepoint.

FEV_1 was measured 15, 30 and 60 min after treatment and then every 30 min up to 4 h. The highest value of three manoeuvres was retained. As a deep inspiration, necessary for the FEV_1 manoeuvre, may influence bronchial tone over several min, response during the first 15 min after inhalation of the drug was only assessed by the measurement of *SGAW*.

All adverse events occurring during the study were recorded.

STATISTICAL ANALYSIS

The speed of onset of action of study treatment following methacholine challenge was characterized by the pattern of change in *SGAW*, *RAW*, and FEV_1 . Time to attain maximum value, and the area under the response curve at 5 min, following challenge were compared. In addition, mean values of *SGAW*, *RAW* and FEV_1 at each timepoint were compared. Comparisons of times taken to achieve specified levels of each of these variables (e.g. time to reach twice postchallenge levels of *SGAW*) were planned but could not be made due to lack of power. In the event, there was no evidence that order of delivery of active treatment had any impact on speed of onset of action, the time delay between

TABLE 1. Characteristics of the 24 patients in the study

Gender F/M	6/18
Age (years)	52 ± 6
Height (cm)	171 ± 8
Weight (kg)	78 ± 16
FEV ₁ at baseline (l)	2.00 ± 0.56
FEV ₁ at baseline (% pred)	62 ± 14
Reversibility (% baseline FEV ₁)	39 ± 17
SGAW at baseline (kPa ⁻¹ s ⁻¹)	0.45 ± 0.17
PD ₂₀ FEV ₁ median (μg methacholine)	43 (range 0–1493)

Values are presented as mean ± SD. F, female; M, male; FEV₁, forced expiratory value in 1 s; % pred, percentage of predicted value; SGAW, specific airway conductance; PD₂₀ FEV₁ dose of methacholine causing a fall in FEV₁ of 20% of baseline value.

treatments (active–placebo pair) being much smaller than the time taken to achieve significant recovery following challenge. Accordingly, patient response was characterized as the average over pairs of study days where the same active treatment was given. Comparisons between treatments were made using analysis of covariance (ANCOVA) controlling for postchallenge baseline values, as well as study period and patient differences. There were no grounds *a priori* for expecting carry-over treatment effect given the relatively short half-life of the two study drugs compared to the relatively long interval between study days. Accordingly we did not allow for the possible effect of carry-over in analysis. The analysis was carried out using SAS[®] proc GLM. Values of SGAW, RAW and FEV₁ were log-transformed prior to analysis.

Results

DEMOGRAPHICS AND BASELINE MEASUREMENTS

Twenty-seven patients were enrolled in the study. Three of these patients withdrew from the study prior to randomization and are therefore not included in the intent-to-treat analysis. The demographic data and baseline lung function of the 24 patients who participated in the study are given in Table 1. Twenty-three were receiving asthma medication, mostly an inhaled β₂-agonist (23) and an inhaled steroid (18). All patients randomized to receive treatment completed the methacholine challenge on four occasions as required by the protocol. Premethacholine challenge values of SGAW, RAW and FEV₁ (Table 2) and PD₂₀ FEV₁ remained relatively stable throughout the study.

SPECIFIC AIRWAY CONDUCTANCE (SGAW)

Levels of SGAW were slightly, but consistently, higher following treatment with salbutamol as compared to formoterol at all timepoints over the first 2 h. Comparing treatments at each timepoint in turn, this difference only

TABLE 2. Mean (± SD) values of SGAW, RAW and FEV₁ immediately before methacholine challenge

Treatment	SGAW (kPa ⁻¹ s ⁻¹)	RAW (kPa l ⁻¹ s ⁻¹)	FEV ₁ (l)
Salbutamol	0.47 ± 0.18	0.47 ± 0.15	1.91 ± 0.49
Formoterol	0.44 ± 0.17	0.51 ± 0.17	1.87 ± 0.53

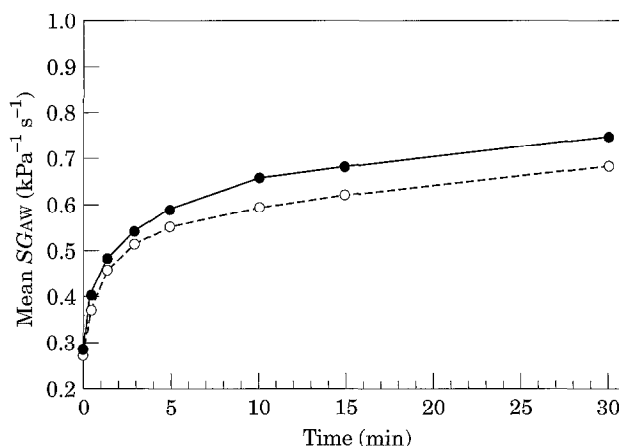


FIG. 1. Mean values of specific airway conductance (SGAW) during the first 30 min after salbutamol (●—●) and formoterol (○—○).

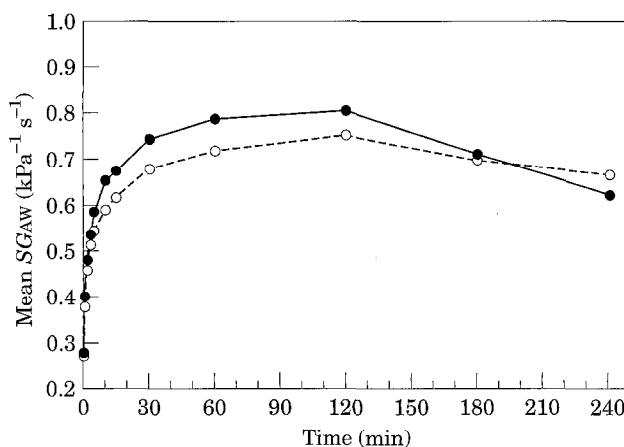


FIG. 2. Mean values of specific airway conductance (SGAW) over 4 h after salbutamol (●—●) and formoterol (○—○).

reached statistical significance at 10 and 15 min after treatment ($P < 0.05$) (Figs 1, 2).

However, comparisons of AUC, which represents a weighed average of SGAW values, show how the consistent direction of the treatment differences accumulates to give a stronger overall level of statistical evidence. By 15 min the AUC difference was statistically significant ($P = 0.04$) and gave an estimated difference in mean SGAW levels of 0.59 kPa⁻¹ s⁻¹ for salbutamol compared to 0.55 kPa⁻¹ s⁻¹ for formoterol over this period.

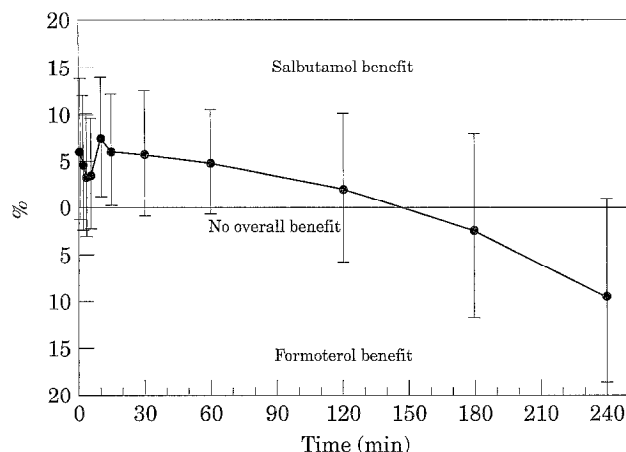


FIG. 3. Mean difference (95% CI) in $SGAW$ after salbutamol or formoterol, expressed as a percentage of the maximum achieved and adjusted for differences in $SGAW$ following methacholine challenge and for the effects of patient and visit.

From Fig. 1 it can be derived that salbutamol produced a two-fold increase in $SGAW$ within 4 min, compared to 5 min for formoterol. Both salbutamol and formoterol achieved pre-methacholine $SGAW$ values within 3 min. There was no significant difference between the maximum values for $SGAW$ after inhalation of the two drugs, with increases of 184% after salbutamol and 176% after formoterol. The mean time taken for salbutamol to induce a maximal increase in $SGAW$ was 79.3 min compared to 119.6 min after formoterol [$P < 0.01$, 95% confidence interval (CI) - 64.6 - 16.1]. As the curves were fairly flat, the actual maximum occurred relatively late. After 4 h $SGAW$ level was higher following formoterol than after salbutamol.

When the data were expressed alternatively at each timepoint as a percentage of the maximum increase in $SGAW$, salbutamol showed a small, but consistent benefit over the first 2 h after administration of the drugs, being statistically significant 10 and 30 min after inhalation ($P < 0.05$) (Fig. 3).

SPECIFIC AIRWAY RESISTANCE (RAW)

The differences in RAW between salbutamol and formoterol reflected the differences in $SGAW$; RAW was approximately 5% and 2% lower following salbutamol when expressed in absolute terms over the first 60 min and as a percentage of the maximum decrease over the first 120 min. For the latter comparison, this reached statistical significance after 60 min ($P < 0.05$). Furthermore, the time taken for salbutamol to induce a maximal decrease in RAW occurred significantly earlier than with formoterol. The mean maximal decreases in RAW occurred 69.6 min after salbutamol compared to 112.8 min after formoterol ($P < 0.01$; 95% CI - 70.4 - 15.9). The time taken to achieve a two-fold decrease in RAW was statistically significantly faster for salbutamol ($P < 0.05$).

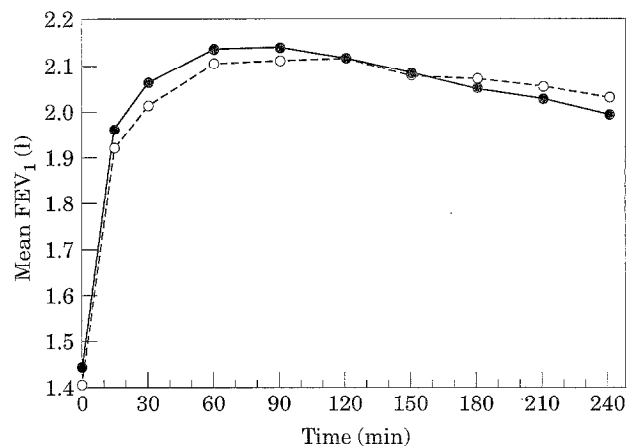


FIG. 4. Mean values of forced expiratory volume in 1 s (FEV_1) over 4 h after salbutamol (●—●) and formoterol (○—○).

FORCED EXPIRATORY VOLUME IN 1 S (FEV_1)

FEV_1 values were also greater (approximately 2%) following salbutamol over the first 2 h when expressed as a percentage of the maximal increase although there was no difference between the two treatments in terms of absolute FEV_1 values (Fig. 4).

TOLERABILITY

Both drugs were well tolerated and no adverse events were reported.

Discussion

This study compared the onsets of action of the recommended dose of salbutamol (200 μ g) and formoterol (12 μ g) in reversing methacholine-induced bronchoconstriction. The results suggest that the onset of action of salbutamol is slightly faster than that of formoterol. This was demonstrated in several ways. Changes in $SGAW$ and RAW were slightly but consistently higher during the first 2 h after inhalation of salbutamol, both in absolute values and as percentages of the maximum response. Furthermore, both the time to reach a specified increase in $SGAW$ and the time to attaining a maximum level of $SGAW$ were shorter after salbutamol than after formoterol.

Four clinical studies have compared the time courses of the bronchodilatory effects of salbutamol and formoterol. Derom *et al* (3), Wallin *et al* (4) and Van Noord *et al* (6) used $SGAW$ as the pharmacodynamic endpoint whilst Beach *et al* (10) used FEV_1 . Measurements of $SGAW$ offer two advantages. First, they are a more sensitive index of changes in airway calibre than FEV_1 (11,14). Second, they avoid a deep inspiration, necessary for the FEV_1 manoeuvre, which has variable effects on the magnitude and direction of change in airway calibre in asthmatic subjects, depending on changes in the relative degree of hysteresis of airways and parenchyma (15). The studies

which used SGAW as the endpoint produced conflicting results: Wallin *et al* (4) and Van Noord *et al* (6) suggested that the two drugs had similar onset times whilst in the study by Derom *et al* (3) salbutamol had a faster onset of action when the data were expressed either as a percentage of the maximum response or as time to maximum response. It can be argued that these studies were not performed under conditions which simulate acute bronchoconstriction and it is difficult to study spontaneously occurring bronchoconstriction repeatedly in a controlled way (9). The study by Beach *et al* (10), which did use a controlled bronchoconstriction model, concluded that salbutamol and formoterol at both 12 μ g and 24 μ g produced marked bronchodilator effects within 2 min and reached a peak within 10 min but detected no significant differences between the treatments. However, as discussed above the study used the relatively insensitive and less appropriate FEV₁ as an endpoint.

Furthermore, when looking at the shape of the curves of formoterol 12 μ g and salbutamol 200 μ g, salbutamol is also consistently higher than formoterol 12 μ g, which is in line with our findings. The present study is the first to compare salbutamol and formoterol using SGAW as the endpoint and using methacholine challenge to induce a standardized level of bronchoconstriction.

In designing the present study other challenge tests were considered: although exercise and allergen are less artificial and more closely analogous to naturally occurring bronchoconstriction, methacholine challenge was selected because of its greater sensitivity and the fact that it has been shown to be predictive of the allergen response (16). Measurements were performed when the fall in FEV₁ was at least 20% of the baseline value after methacholine and had reached a plateau for at least 3 min. Cartier *et al* (17) demonstrated that the mean duration of this plateau phase was 75 min (range 12–150). This suggests that measurements during the first 15 min purely reflect the effects of the drugs investigated, whereas later spontaneous recovery of bronchoconstriction can interfere. However, by comparing the two time–response curves the latter effect is eliminated.

Malo *et al* (18) concluded that after a methacholine test the response to an inhaled β_2 -agonist was less than in a situation of spontaneous airway obstruction. Merkus *et al* (19) found that after histamine challenge and subsequent spontaneous recovery a higher dose of salbutamol was required to obtain the same bronchodilatation as on the control day. These authors suggested that the effects of bronchial challenge on the airway wall could limit or delay the bronchodilator response. Our study indicates that the onset of action of β_2 -agonists after methacholine-induced bronchoconstriction is not affected and seems similar to a situation of spontaneous airway obstruction.

The present study, in common with previous studies, has demonstrated that differences between the time courses of salbutamol and formoterol are small, statistically significant differences between them being achieved only at 10 and 15 min after treatment. This is the first study to assess the effect of treatment within the first min and furthermore a total of four assessments of lung function were made within the first 5 min. We believe that the fact that salbutamol

begins to demonstrate a more rapid effect than formoterol during this time period, even if the difference is small, can be important to a patient suffering from an acute attack of bronchoconstriction. Using SGAW as an endpoint the study demonstrated a difference in time of 1 min to a twofold increase (4 min salbutamol vs 5 min formoterol).

We conclude that in methacholine-induced bronchoconstriction, which can be considered as a model of an acute asthma attack, both salbutamol and formoterol have a very rapid onset of action, salbutamol being slightly faster.

At present, in most guidelines (20) short-acting β_2 -agonists are indicated for episodic bronchoconstriction and long-acting β_2 -agonists are recommended as maintenance therapy when standard doses of inhaled corticosteroids fail to achieve control of asthma (17). We believe that the present study is supportive of this strategy.

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